REMARKS

Claims 1-4, 7-12, 14, 18-22, and 24-26 are pending in the application. By the present communication, claims 1-3, 11, 12, 18-21, 25, and 26 have been amended. These amendments add no new matter as the claim language is fully supported by the specification and original claims. Accordingly, entry of this amendment is respectfully requested. Subsequent to the entry of the present amendment, claims 1-4, 7-12, 14, 18-22, and 24-26 are pending and at issue.

I. Claim Objection

The objection to claims 20-22 and 24 for allegedly containing an informality is respectfully traversed. Specifically, the Examiner asserts that the "isolating" and "extracting" steps of claim 20 are not separated by punctuation. Without acquiescing to the reasoning offered in the Action, claim 20 has been amended herein to include a semicolon between these steps, consistent with the Examiner's suggestion. Accordingly, reconsideration and withdrawal of this objection are respectfully requested.

II. Rejections under 35 U.S.C. §112, First Paragraph (enablement)

Claims 1-4, 7-12, 14, 18-22, and 24-26 are rejected under on 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make or use the invention. Applicants respectfully traverse the rejection as it applies to the pending claims.

The present claims are directed to methods of detecting the presence of defined target neoplastic nucleic acids having mutant nucleotide sequences, which are present in a primary neoplasm, in histologically normal tissue specimens. These methods provide the advantage of detecting the infiltration or migration of a small number of tumor cells into normal tissue *before*

such cells are able to grow into a tumor that is visible by standard histologic methods. Thus, such methods can be used as "an adjunct to cytopathology" (specification at p. 4, lines 18-20) and allow the detection of tumor cells in sites external to the primary tumor, which might otherwise go undetected.

Accordingly, the present invention, as defined by, for example claim 1, is directed to a method of detecting a mutant nucleotide sequence of a neoplastic nucleic acid (*e.g.*, APC, DCC, NF1, NF2, RET, VHL, or WT-1) that "is present in the primary neoplasm," in nucleic acids extracted from a tissue specimen, which is "external to the neoplasm" and is "histologically normal." As discussed previously, the specification provides abundant guidance for the practice of the claimed methods as well as a detailed working example. Thus, based on this disclosure, one of skill in the art would have reasonably expected that mutations in any of the other recited tumor suppressor genes, which are found in the primary tumor, could similarly be detected in normal-appearing tissues into which tumor cells from the primary tumor had migrated.

Therefore, in order to practice the claimed method, the skilled artisan simply need know whether one or more of the target neoplastic nucleic acids is present in a mutated form in the primary neoplasm. As stated in the specification at for example Table 1, and as is known in the art, tumor suppressor genes (e.g., APC, DCC, NF1, NF2, RET, VHL, and WT-1) and mutated forms thereof have been associated with specific cancer types. Armed with this knowledge, the skilled artisan can readily assay the neoplasm and a histologically normal tissue specimen for the mutant nucleotide sequence of the relevant tumor suppressor gene using the methods exemplified for p53.

Moreover, reports in the literature published after the filing of the application support the operability of the present methods. In one study, Wang and colleagues (World J Surg 28(7):721-6, 2004; abstract attached) assayed cancer tissues and paired serum samples for APC, K-ras, and p53 gene mutations obtained from 104 patients having colorectal cancer. The authors demonstrate that mutated forms of each of these markers can be detected in serum (*i.e.*, a tissue

external to the primary neoplasm) of these patients, but not in the serum of normal, healthy control subjects. Moreover, it was further shown that detection of any of these markers in serum is correlated with higher rate of postoperative metastasis/recurrence than those patients having serum that was negative for the markers.

The Action appears to base this rejection, in part, on an alleged unpredictability regarding "whether specimens taken from these locations [*i.e.*, lymph nodes and or/tumor margin tissues] that were found to contain detectable levels of such 'target neoplastic' nucleic acids would in fact appear histologically normal" (Office Action at page 6). It is respectfully submitted that tissues that do *not* appear histologically normal would not be tested by the present methods. Indeed, doing so would only confirm the migration of the tumor to these other tissues, which was apparent by microscopy. Furthermore, it has been demonstrated in the literature that histologically normal tissues can indeed harbor detectable levels of markers associated with a primary tumor. In a study by Bilchik et al., (J Clin Oncology 19(4):1128-36, 2001; copy attached), sentinel nodes from 40 patients with colorectal cancer were analyzed by standard hematoxylin and eosin (HE) staining and cytokeratin immunohistochemical (CK-IHC) staining, in addition to RT-PCR for detection of tumor markers. In this study it was shown that, of 26 patients with no evidence of sentinel node involvement as determined by HE or CK-IHC, *twelve* of these patients were found to have occult micrometastases as determined by RT-PCR detection of tumor markers.

The Action further contends that there were many types of microscopy available to those in the art including additional techniques that may be employed to increase the sensitivity of such methods. It is respectfully submitted that the sensitivity of the microscopy methods is not relevant to the present methods. Indeed, as discussed above, such microscopy methods having increased sensitivity would serve to identify tissues that would *not* require testing by the present methods. Rather, the present methods are concerned with detection of mutant nucleotide sequences in tissues that appear histologically normal.

In summary, it is submitted that one skilled in the art, in view of the present specification and that which was known in the art, would reasonably have predicted that the disclosed methods could be applied to the detection of a mutant form of any of the recited tumor suppressor genes, wherein that same mutation is present in the primary tumor, in histologically normal tissues harboring a small number of metastasized tumor cells from the primary tumor. Accordingly, the skilled artisan would have known how to practice the claimed methods without undue experimentation.

Accordingly, withdrawal of rejection of claims 1-4, 7-12, 14, 18-22, and 24-26 under 35 U.S.C. §112, first paragraph is respectfully requested.

III. Rejections under 35 U.S.C. §112, Second Paragraph

Claim 19 stands rejected under 35 U.S.C. §112, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Applicants respectfully traverse the rejection as it applies to the pending claims.

The Examiner asserts that claim 19 is indefinite because it is allegedly unclear whether the claim is drawn to a method for detecting a mammalian target neoplastic nucleic acid having a mutant nucleotide sequence in a tumor margin tissue specimen or to a method of detecting such a nucleic acid in any tissue specimen that appears histologically normal. Without acquiescing to the reasoning offered by the Examiner and to expedite prosecution, this claim has been amended herein to further clarify that the tissue specimen is a tumor margin tissue specimen. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants ' undersigned representative if there are any questions relating to this application.

The Commissioner is hereby authorized to charge $120.00 as payment for the Petition for One-Month Extension of Time fee to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,

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Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer No. 28213

Attachments: Wang *et al.*, World J Surg 28(7):721-6, 2004, abstract
Bilchik *et al.*, J Clin Oncology 19(4):1128-36, 2001